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STEREOCHEMISTRY OF MONO-TETRAHYDROFURANYL MOIETY IN CYTOTOXIC POLYKETIDES. PART A: SYNTHESIS OF MODEL COMPOUNDS

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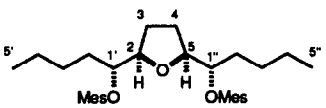
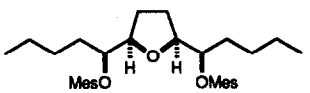
Abstract. Dimesitoate esters of α,α-dibutyl-2,5-tetrahydrofurandimethanols of different relative stereochemistry were prepared. They serve as model compounds for a ^{1}H-NMR-based stereochemical analysis of the mono-tetrahydrofuranyl moiety of cytotoxic polyketides.

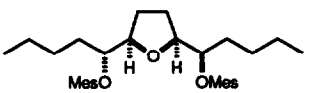
Recently, pattern recognition approaches based on ^{1}H-NMR chemical shift differences had been devised in assigning the relative[1a,1b] and the absolute[1c] stereochemistry of the bis-tetrahydrofuranyl moiety of cytotoxic polyketides such as uvaricin,[2a] asimicin,[2b] rolliniastatin,[2c] bullatacin and bullatacinone.[2d] However, no systematic study has been carried out to address the assignment of those polyketides containing a mono-tetrahydrofuran (mono-THF) ring adjoined to hydroxyalkyl groups at the 2,5-positions.[3] Therefore, a novel ^{1}H-NMR-based method is devised to assign the relative stereochemistry of the mono-THF moiety of cytotoxic polyketides. The synthesis of the model compounds **1** - **6** is described in this letter.[4]



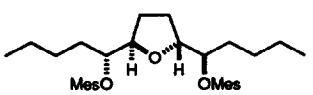
1 (*thr-cis-thr*)



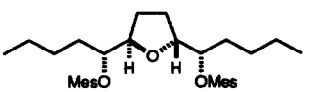
2 (*ery-cis-ery*)



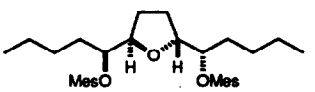
3 (*thr-cis-ery*)



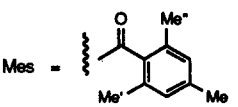
4 (*thr-trans-thr*)



5 (*thr-trans-ery*)

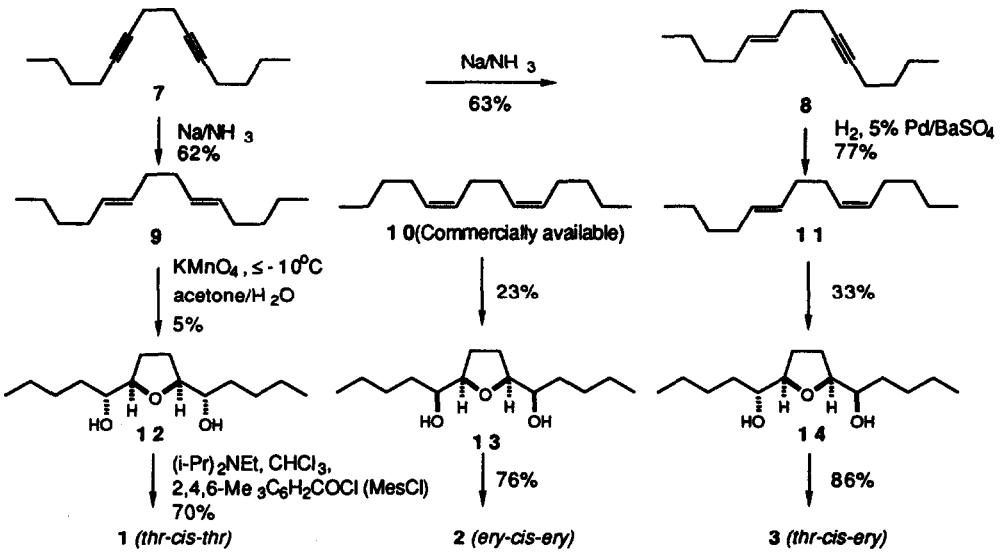


6 (*ery-trans-ery*)



trans,trans-Diene **9** was prepared by reduction of diyne **7** with Na/NH_3.[5] *cis,cis*-Diene **10** is commercially available.[6] *trans,cis*-Diene **11** was prepared from diyne **7** by reduction with Na/NH_3 to give *trans*-enyne **8** and subsequent reduction with Pd/$BaSO_4$.[7a] The symmetrical *cis* diols **12** (*thr-cis-thr*) and **13** (*ery-cis-ery*) were

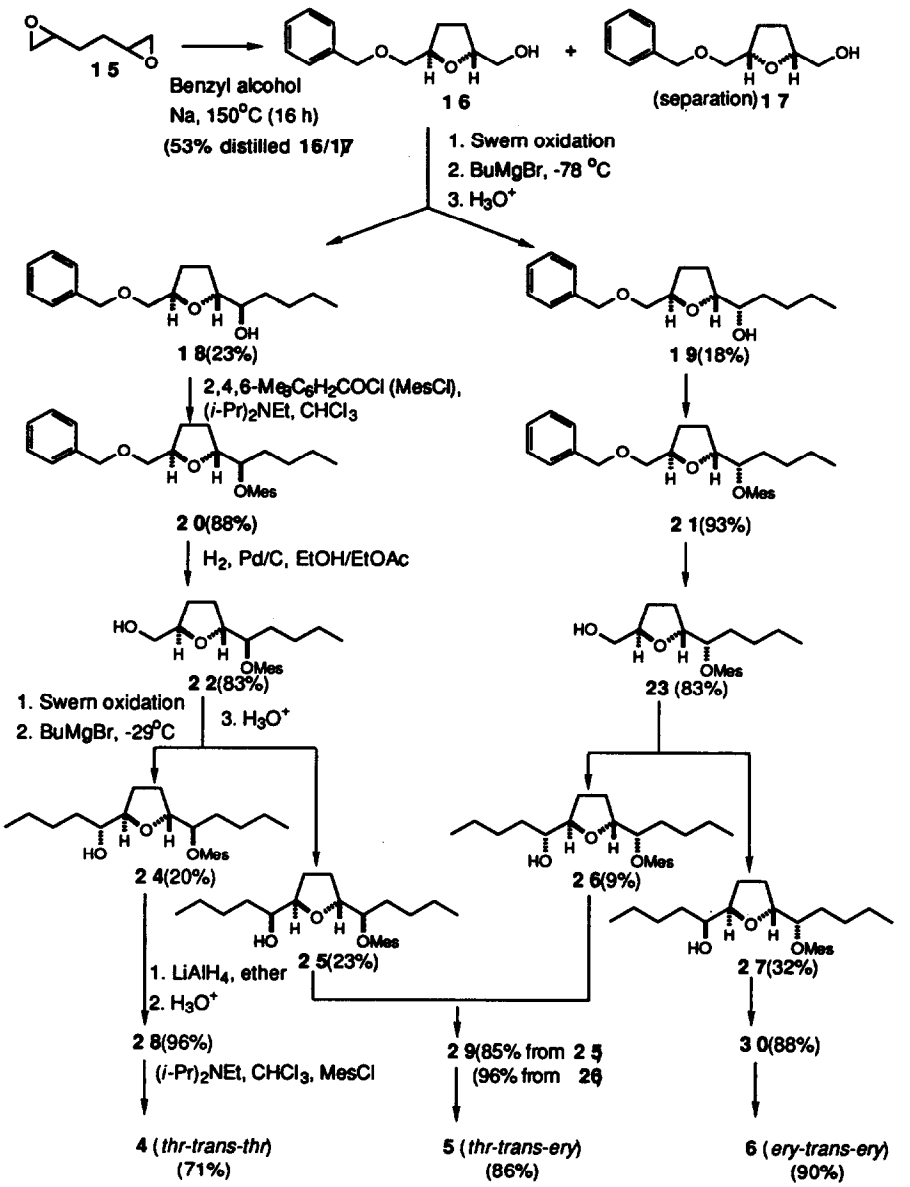
prepared from dienes **9** (*trans, trans*) and **10** (*cis,cis*), respectively, by the general methods according to Klein *et al.*[7b] and Walba and co-workers[7c,d] which stereospecifically give diols with a *cis* ring. The unsymmetrical *cis* diol **14** (*thr-cis-ery*) was prepared by using the *trans,cis*-diene **11** as shown in Scheme 1. The corresponding dimesitoates **1**, **2** and **3** were prepared in $CHCl_3$ from mesitoyl chloride ($2,4,6\text{-}Me_3C_6H_2COCl$).



Scheme 1

Symmetrical *trans* dimesitoates **4** and **6** and unsymmetrical *trans* dimesitoates **5** were prepared from the diepoxide **15** (Scheme 2). A 50:50 mixture of substituted tetrahydrofurans **16** (*trans*) and **17** (*cis*) was prepared based on a literature procedure[8] followed by the separation of the isomers on silica gel.[9,10] Swern oxidation[11] of **16** gave a crude mixture containing approximately 45% of the corresponding aldehyde which was treated with butylmagnesium bromide to give compounds **18** (threo) and **19** (*erythro*), respectively.[12-15] These alcohols were protected using mesitoyl chloride to give the mesitoates **20** and **21**, which were debenzylated by hydrogenation to afford the alcohols **22** and **23**. Compounds **22** and **23** were in turn oxidized to their respective aldehydes which were used without further purification. Addition of butylmagnesium bromide at -29 °C did not give any significant stereoselectivity except in the reaction involving the aldehyde from **23**, in which *threo* and *erythro* analogs **26** and **27** were isolated in yields of 9% and 32%, respectively.[12-15] Alcohols **24**, **25**, **26**, **27** were reduced to diols **28**, **29**, **29**, and **30**, respectively (alcohols **25** and **26** both gave diol **29**), which were subsequently converted to the dimesitoate esters **4** (*thr-trans-thr*), **5** (*thr-trans-ery*) and **6** (*ery-trans-ery*).

The application of the ^{1}H-NMR study of **1-6** will be discussed in the next letter.


15
Benzyl alcohol
Na, 150°C (16 h)
(53% distilled 16/17
16
(separation) 17
1. Swern oxidation
2. BuMgBr, -78 °C
3. H3O+
18(23%)
19(18%)
2,4,6-Me3C6H2COCl (MesCl),
(i-Pr)2NEt, CHCl3
20(88%)
21(93%)
H2, Pd/C, EtOH/EtOAc
22(83%)
23 (83%)
1. Swern oxidation
2. BuMgBr, -29°C
3. H3O+
24(20%)
25(23%)
26(9%)
27(32%)
1. LiAlH4, ether
2. H3O+
28(96%)
(i-Pr)2NEt, CHCl3, MesCl
29(85% from 25
(96% from 26)
30(88%)
4 (thr-trans-thr)
(71%)
5 (thr-trans-ery)
(86%)
6 (ery-trans-ery)
(90%)

Scheme 2

Acknowledgments

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References and Notes

1 (a) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 4402. (b) Hoye, T. R.; Zhuang, Z. *J. Org. Chem.* **1988**, *53*, 5578. (c) Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203.

2 (a) Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R. *J. Org. Chem.* **1982**, *47*, 3152. (b) Rupprecht, J. K.; Chang, C.-J.; Cassady, J. M.; McLaughlin, J. L.; Mikolajczak, K. L.; Weisleder, D. *Heterocycles* **1986**, *24*, 1197. (c) Pettit, G. R.; Cragg, G. M.; Polonsky, J.; Herald, D. L.; Goswami, A.; Smith, C. R.; Moretti, C.; Schmidt, J. M.; Weisleder, D. *Can. J. Chem.* **1987**, *65*, 1433. (d) Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Anderson, J. E.; Smith, D. L.; Chang, C.-J.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 463.

3 (a) McCloud, T. G.; Smith, D. L.; Chang, C.-j.; Cassady, J. M. *Experientia* **1987**, *43*, 947. (b) Alkofahi, A.; Rupprecht, J. K.; Chang, C.-j.; McLaughlin, J. L. *Experientia* **1988**, *44*, 83. (c) Xu, L.; Chang, C.-j.; Yu, J.-G.; Cassady, J. M. *J. Org. Chem.* **1989**, *54*, 5418.

4 While **1** and **2** are meso, **4** and **6** both have rotational symmetry and were prepared as racemates. Unsymmetrical **3** and **5** were also prepared as racemates.

5 Garwood, R. F.; Naser-ud-Din; Scott, C. J.; Weedon, B. C. L. *J. Chem. Soc. Perkin I*, **1973**, 2714.

6 K&K Laboratories, a division of ICN Biomedicals specializing in rare chemicals.

7 (a) Tashner, M. J.; Tosen, T.; Heathcock, C. H. *Org. Synth.* **1985**, *64*, 108. (b) Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353. (c) Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4396. (d) Walba, D. M.; Edwards, P. D. *Tetr. Lett.* **1980**, *21*, 3531.

8 Hauck, F. P.; Jacobs, G. A. (E. R. Squibb & Sons, Inc., Princeton, N. J.) U.S.Patent 4,279,902, July 21, 1981.

9 Alcohols **16** and **17** were reductively debenzylated (H_2, Pd/C) to *trans*- and *cis*-2,5-tetrahydrofurandimethanol, respectively, which are diols of known stereochemistries.[10]

10 (a) Gagnaire, D.; Monzeglio, P. *Bull. Soc. Chim. Fr.* **1965**, 474. (b) Moore, J. A.; Kelly, J. E. *Macromolecules* **1978**, *11*, 568.

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12 It is long known that for a given isomeric pair of α-substituted 2-tetrahydro- furanmethanols the carbinol methine protons give chemical shifts that are considerably upfield for the *threo* analogs compared with the *erythro* counterparts.[13] Thus, alcohols **18** (δ_{CHOH} 3.40), **24** (δ_{CHOH} 3.38) and **26** (δ_{CHOH} 3.37) were assigned *threo* relationships while the counterparts **19** (δ_{CHOH} 3.85), **25** (δ_{CHOH} 3.76) and **27** (δ_{CHOH} 3.79) were assigned *erythro* relationships.

13 (a) Descotes, G.; Lailly, A. *Bull. Soc. Chim. Fr.* **1967**, 2989. (b) Amouroux, R.; Chastrette, F.; Chastrette, M. *J. Heterocyclic Chem.* **1981**, *18*, 565. (c) Mulholland, Jr., R. L.;Chamberlain, A. R. *J. Org. Chem.* **1988**, *53*, 1082.

14 Although the reaction of organometallics with 2-monosubstituted-2-formyltetrahydro-furans might be expected to give stereoselectivity following Cram's rule,[15] little or no stereoselectivity appears to result.[13,15] In our hands, reaction of the aldehydes from either **16** or **22** with *n*-BuMgBr ocurred with little or no stereoselectivity (analysis of the crude confirmed this) while reaction of the aldehyde from **23** with *n*-BuMgBr ocurred with anti-Cram stereoselectivity (analysis of the crude verified this).

15 Amouroux, R.; Chastrette, F.; Chastrette, M. *Bull. Soc. Chim. Fr.* **1981**, *2*, 293.

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